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PEPPER HAMILTON LLP
ONE MELLON CENTER, 50TH FLOOR
500 GRANT STREET
PITTSBURGH, PA 15219

EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,656	SCHULTE ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-20, 24, 26-28, 31, 46, 48-53 and 55* is/are pending in the application.

4a) Of the above claim(s) *14-18 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13,19,20,24,26-28,31,46 and 48-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 13, 2009 has been entered.

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on October 29, 2007 is acknowledged. Applicant has elected without traverse the invention designated as Invention Group II, claims 2-31 and 46, directed to a method of using a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) for the specific modulation of the expression of target genes in cells and/or tissues of the CNS and/or eye, wherein said composition is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier.

Within Group II, Applicant has further elected the restricted neural tissue subgroup, cells and tissues of the eye.

Within Group II, Applicant has elected the following species:

i) wherein the dsRNA molecule is dsRNA molecules between 21 and 23 nucleotides in length, as recited in claim 13,

ii) wherein the promoter is a tissue specific promoter, as recited in claim 20,

iii) wherein the dsRNA is complexed to a micellar structure, as recited in claim 22,

iv) wherein the means by which the dsRNA is administered to the eyeball systemic administration, as recited in claim 26,

v) wherein the eye disease is a degenerative retinal disease, as recited in claim 50, and

vi) wherein the organism is human, as recited in claim 31.

Amendments

In the reply filed February 13, 2009, Applicant has cancelled Claims 1, 21-23, 25, 29-30, 32-45, 47 and 54, withdrawn Claims 14-18 and 55, and amended Claims 2, 5 and 7.

Claims 14-18 and 55 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 2-13, 19-20, 24, 26-28, 31, 46 and 48-53 are under consideration.

Priority

This application is a 371 of PCT/EP03/04002, filed April 16, 2003. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/431,173, filed December 5, 2002, under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). While a certified copy of the foreign patent application EPO 02008671.5, filed April 18, 2002, has been filed with the instant application, a certified English translation has not been provided.

The effective priority date of the instant application is granted as April 18, 2002.

Response to Amendment

a) The Office inadvertently misstated the filing date of the PCT application; and

b) Applicants respectfully request clarification as to whether the Examiner specifically requires a certified English translation of the foreign priority document. If such translation is required by the Examiner, Applicants will attend to the matter.

With respect to a), the Examiner acknowledges that the filing date of PCT/EP03/04002 is April 16, 2003.

With respect to b), Applicant's attention is directed to the rejection under 35 U.S.C. 102(e) as being anticipated by Tolentino et al (U.S. Patent No. 7,148,342 B2). Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application. A certified translation of every foreign benefit application or Patent Cooperation Treaty (PCT) application not filed in English is required. 35 U.S.C. 119(b)(3) and 372(b)(3) and 37 CFR 155(a)(4). If no certified translation is in the official record for the application, the examiner must require the applicant to file a certified translation. The applicant should provide the required translation if applicant wants the application to be accorded benefit of the non-English language application. Any showing of priority that relies on a non-English language application is *prima facie* insufficient if no certified translation of the application is on file. 37 CFR 41.154(b) and 41.202(e).

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the February 13, 2009 response will be addressed to the extent that they apply to current rejection(s).

Claim Objections

1. **The prior objections to Claims 5 and 7 are withdrawn** in light of Applicant's amendments to the claims.

2. **Claim 2 is objected to because of the following informalities**: the claim recites the term "oligoribonucleotides" (line 1) and the phrase "dsRNA consisting of 21 to 23 nucleotides". The examiner respectfully suggests amending the preamble (oligoribonucleotides) to be concordant with the actual method step performed (dsRNA) because while dsRNA is an oligoribonucleotide, the term "oligoribonucleotides" reasonably encompasses an enormous genus of nucleic acids structurally distinct from dsRNA.

Appropriate correction and/or clarification is required.

3. **Claim 13 is objected to under 37 CFR 1.75(c),** as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

In the instant case, Claim 2 recites the dsRNA molecules consist of 21 to 23 nucleotides. Dependent Claim 13 recites the dsRNA molecules "are between" 21 to 23 nucleotides in length. Thus, the dsRNA molecules of Claim 13 are the same length as the dsRNA molecules of Claim 2.

Appropriate correction and/or clarification is required.

4. **Claim 24 is objected to because of the following informalities**: the claim recites dependency on cancelled Claim 21. In the interest of compact prosecution, and in light of

Applicant's amendments to the claims moving limitations of previous Claim 21 into Claim 2, the Examiner interprets instant Claim 24 to be dependent upon Claim 2.

Appropriate correction and/or clarification is required.

Claim Rejections - 35 USC § 112

5. **The prior rejection of Claims 5-6 and 50-53 under 35 U.S.C. 112, first paragraph, is withdrawn** in light of Applicant's argument that the present application discloses working examples that disclose that "systemic administration by tail vein injection or local administration by retrobulbar injection . . . of naked dsRNA" is able to inhibit expression of a target gene that is expressed behind the blood-brain or blood-retina barrier (Final Office Action, page 6). The Office does not question the enablement of these working examples, and based upon these teachings one of skill in the art would not require undue experimentation to practice the claimed invention. Upon further review and consideration of the specification and the claims, the examiner finds this argument persuasive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. **Claims 2, 7, 13, 24, 26-28 and 31 stand and Claims 5, 8-12 and 50 are newly rejected under 35 U.S.C. 102(b)** as being anticipated by Carter (U.S. Patent No. 5,712,257), as evidenced by Rummelt et al (Opthalmology 101(2):270-279, 1994; Abstract only).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed February 13, 2009.

Claim interpretation: Applicant claims the method for delivery of oligoribonucleotides comprises introducing "a composition comprising one or more naked double-stranded oligonucleotides (dsRNA). However, the term "comprising" is open-ended and allows for additional, unrecited elements in the claims. MPEP §2111.03 specifically sets forth that the transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and **does not exclude** additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). In the instant case, the specification discloses that the naked dsRNAs can be introduced into the cells or tissues combined with one or more suitable carriers, e.g. a micellar structure, preferably a liposome (pg 13, ¶1). Thus, the broadest reasonable interpretation of the instant claims reasonably embraces "a composition comprising" a carrier vehicle, e.g. micelle or liposome, encapsulating naked dsRNA molecules.

With respect to Claim 2, Carter discloses a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier. Carter disclose "naked dsRNA" to achieve a degree of efficacy (Table 2). Carter discloses the naked dsRNA is complexed with liposomes (col. 13, lines 49-50) or with a surfactant forming a micelle (col. 1, lines 55-56), wherein the surfactant may be anionic, cationic or non-ionic (col. 1, lines 63-64; col. 3, lines 20-42; Tables 1-2).

With respect to Claims 2, 7, 24 and 26, Carter discloses that the art has practiced administering dsRNA by injection into a patient's bloodstream (col. 1, lines 37-38) and that the composition may also be topically administered (col. 7, line 1), in a form to be applied outside the eyeball, e.g. eye drops (col. 7, line 34). Thus, the carrier and/or dsRNA-binding molecules were selected such that the dsRNA molecules are delivered continuously to the target cells or tissues over a defined period of time.

With respect to Claims 2, 5, 8-12 and 50, Carter discloses the intended use of the pharmaceutical compositions comprising dsRNA are to treat or prevent viral infections, e.g. herpes virus, HIV, CMV (col. 7, lines 13-31), wherein those of ordinary skill in the art recognize that herpes viruses, HIV and/or CMV infects retinal tissues of the eye, as evidenced by Rummelt et al teaches triple retinal infection with HSV, HIV and CMV, wherein the retina, neurosensory retina, vascular endothelium and retinal pigment epithelium were affected. Thus, those of

ordinary skill in the art would immediately recognize that Carter implicitly teaches "in need thereof", and that the viral target genes expressed in infected retinal tissues are necessarily "expressed behind the blood-brain or blood-retina barrier", and thus specific for said infected retinal cells and tissue.

With respect to Claim 13, Carter discloses the dsRNA may be between 21-23 nucleotides in length (col. 7, line 51-col. 8, line 14).

With respect to Claims 27-28 and 31, Carter discloses the cells, tissue or organism may be mammalian, e.g. mouse or human (col. 3, line 18; col. 6, line 33; col. 7, line 17; col. 8, line 43), wherein one of ordinary skill in the art recognizes mammals to be vertebrates.

Response to Arguments

Applicant argues that:

a) the claims are now amended to recite a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier an organism in need thereof comprising introducing a composition comprising one or more naked double-stranded oligoribonucleotides (dsRNA) consisting of 21 to 23 nucleotides. Carter states that a "key to the present invention is the building of a micelle on or around the dsRNA" (Col. 3, lines 64-65). This key feature of Carter would not include naked dsRNA;

b) Carter reference states that "naked dsRNA has a high negative charge and may be physically repulsed by the cell." Accordingly, the Carter reference fails to teach the introduction of naked dsRNA as recited in the pending claims;

c) the Carter reference fails to disclose a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier to an organism in need thereof; and

d) the amendment to the claim that recites "in need thereof' requires that the person performing the method recognize the need to traffic the dsRNA molecule across the blood-brain or blood-retina barrier. Since the Carter reference fails to have any recognition or intent to traffic a dsRNA molecule across the blood-brain barrier, the Carter reference also fails to teach this element. The Carter reference fails to disclose or suggest that it would be possible to traffic a dsRNA across the blood-brain or blood-retina barrier.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), Applicant claims the method for delivery of oligoribonucleotides comprises introducing "a composition comprising one or more naked double-stranded oligonucleotides (dsRNA). However, the term "comprising" is open-ended and allows for additional, unrecited elements in the claims. MPEP §2111.03 specifically sets forth that the transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and **does not exclude** additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). In the instant case, the specification discloses that the naked dsRNAs can be introduced into the cells or tissues combined with one or more suitable carriers, e.g. a micellar structure, preferably a liposome (pg 13, ¶1). Thus, the broadest reasonable interpretation of the instant claims continues to reasonably embrace the Carter micelles encapsulating naked dsRNA molecules, wherein said dsRNA molecules are reasonably interpreted to be "naked" to the extent that the dsRNA is not chemically modified, e.g. Tables 1-2, or have not been previously encapsulated by another structural ingredient. Furthermore, Applicant appears to overlook that Carter discloses the administration of "naked dsRNA" in the absence of a surfactant carrier, wherein the administration of naked dsRNA can demonstrate a degree of efficacy (Table 2). Applicant fails to specifically exclude the one or more suitable carriers, e.g. a micellar structure or liposome, from the composition comprising the dsRNA in the claims.

With respect to b), Applicant appears to overlook that Carter discloses the administration of "naked dsRNA" to cells in the absence of a surfactant, wherein the administration of naked dsRNA can demonstrate a degree of efficacy (Table 2).

With respect to c), Carter discloses the intended use of the pharmaceutical compositions comprising dsRNA are to treat or prevent viral infections, e.g. herpes virus, HIV, CMV (col. 7, lines 13-31), wherein those of ordinary skill in the art recognize that herpes viruses, HIV and/or CMV infects retinal tissues of the eye, as evidenced by Rummelt et al who teaches triple retinal infection with HSV, HIV and CMV. Thus, those of ordinary skill in the art would immediately recognize that Carter implicitly teaches "in need thereof".

With respect to d), the trafficking of the dsRNA across the blood-brain or blood-retina barrier naturally flows from the administration of the composition comprising the naked dsRNA

molecules. Such trafficking is considered an inherent and natural feature of the biological system, that is to say, normal physiology and cell biology. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Furthermore, see *Eli Lilly & Co. v. Barr Labs.*, Inc., 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art". Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In the instant case, Carter discloses that the art has practiced administering dsRNA by injection into a patient's bloodstream (col. 1, lines 37-38) and that the composition may also be topically administered (col. 7, line 1), in a form to be applied outside the eyeball, e.g. eye drops (col. 7, line 34). Carter et al discloses means of administering dsRNA by the same means to the same cells or tissues of the eye and has disclosed the active method steps recited in the claims. Thus, absent evidence to the contrary, the dsRNA of Carter et al administered by injection into a patient's bloodstream or topically, e.g. eye drops, would inherently and necessarily traffick across the blood-brain or blood-retina barriers.

7. **The prior rejection of Claims 2-3, 5-10, 13, 19-22, 24, 26-28, 31 and 50-54 stand rejected under 35 U.S.C. 102(a) and 35.U.S.C 102(e)** as being anticipated by LaFleur et al (U.S. Patent No. 6,433,145 B1) **is withdrawn** in light of Applicant's amendment to Claim 2 reciting the administration of a dsRNA consisting of 21-23 nucleotides, a limitation that LaFleur et al do not disclose.

8. **Claims 2-13, 24, 26-28, 31, 46, 50 and 54 stand, and Claims 19-20 and 48 are newly rejected under 35 U.S.C. 102(a) and 35.U.S.C 102(e)** as being anticipated by King (U.S. 2002/0165158 A1), as evidenced by Caplen (Trends in Biotech. 20(2):49-51, 2002).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed February 13, 2009.

Claim interpretation: Applicant claims the method for delivery of oligoribonucleotides comprises introducing "a composition comprising one or more naked double-stranded oligonucleotides (dsRNA). However, the term "comprising" is open-ended and allows for additional, unrecited elements in the claims. MPEP §2111.03 specifically sets forth that the transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and **does not exclude** additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). In the instant case, the specification discloses that the naked dsRNAs can be introduced into the cells or tissues combined with one or more suitable carriers, e.g. a micellar structure, preferably a liposome (pg 13, ¶1). Thus, the broadest reasonable interpretation of the instant claims reasonably embraces "a composition comprising" a carrier vehicle, e.g. micelle or liposome, encapsulating naked dsRNA molecules.

With respect to claim 2, King discloses a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue (pg 1, [0009]).

King discloses that the methods are designed to treat angiogenesis-related disorders, e.g. retinopathy, and thus those of ordinary skill in the art would immediately recognize that the organism is in need" of treatment (Abstract; [0010]).

King also discloses the dsRNA molecule to be 21-23 nucleotides in length are recognized in the art to specifically inhibit gene expression [0129].

With respect to claim 3, King discloses the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal model (pg 4, [0039], [0060]; pg 5, [0081-82]), wherein the agent may be administered over a long-term period (pg 4, [0049]).

With respect to claims 4 and 46, King discloses the method provides for the identification or validation of the function of a gene and drug discovery, the method further comprising

comparing the resulting phenotype produced in the test cell, tissue or organism with that of a suitable control, thus allowing information on the function of the gene to be gained. The method may be used to evaluate an agent, e.g. screening for an agent, the method comprising determining if the agent modulates the expression of a target gene (pg 5, [0075], [0082]). Abnormal expression levels in the subject are compared to a control (pg 5, [0066], [0084]).

With respect to claims 5-6, King discloses the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode Protein Kinase C (PKC) isoforms or Retinoblastoma (Rb) (pg 1, [0006]; pg 3, [0026]).

With respect to claims 7-9, King discloses the agent is targeted to retinal tissue (pg 3, [0033]),

With respect to claim 10, King does not recite the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of King reasonably embraces such limitations, absent evidence to the contrary.

With respect to claims 11-12, King does not dislose that PKCβ and/or Rb are predominantly expressed in retinal cells or tissues. However, at the time of the invention, one of ordinary skill in the art recognized that PKCβ and Rb are highly expressed in retinal cells.

With respect to claims 19-20, King discloses the inventive nucleic acids may be inserted into vectors, wherein the expression of the nucleic acid is operably linked to a promoter, e.g. a cell or tissue-specific promoter ([0017], [0025], [0111], [0192]).

With respect to claim 54, King discloses the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (pg 10, [0126]; pg 16, [0183-0194]; pg 18, [0202]), and wherein the carrier may be specific for the retinal cells, e.g. as eyedrops and/or liposomes tagged with antibodies against cell surface antigens of the target tissue (pg 10, [0124-0127]; pg 18, [0202]).

With respect to claim 24, King discloses the carrier may comprise compounds that achieve controlled release (pg 17, [0191]), wherein the period over which the agent is administered can be long term (pg 3, [0036]).

With respect to claim 26, King discloses the agent may be administered by different routes, e.g. intravenous or administered to the eye as eyedrops (pg 10, [0124-0127]).

With respect to claims 27-28 and 31, King discloses the subject may be human (pg 2, [0021]).

With respect to Claim 48, Although King does not disclose *ipsis verbis* that the dsRNA contains two symmetrical 3' overhangs of two nucleotides in length, King does disclose the dsRNA molecule to be 21-23 nucleotides in length are recognized in the art (Caplen, 2002) to specifically inhibit gene expression [0129], wherein Caplen teaches that small dsRNAs of 21-23 nucleotides in length contains two symmetrical 3' overhangs of two nucleotides in length (pg 50, col. 2, ¶2). Thus, those of ordinary skill in the art would immediately recognize that the dsRNA

molecules consisting of 21-23 nucleotides in length inherently possess two symmetrical 3' overhangs of two nucleotides in length, as such was commonly known in the art.

With respect to claim 50, King discloses the inhibition of the target gene expression is associated with retinal disease, e.g. ischemic retinopathy and retinopathy-of-prematurity, (pg 1, [0010], pg 4, [0059]).

Response to Arguments

Applicant argues that the King reference fails to disclose a method for delivery to an organism in thereof comprising a naked dsRNA consisting of 21 to 23 nucleotides. Therefore, the claims are not anticipated because the King reference fails to teach each and every element of the claim.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant appears to have overlooked that King discloses that the methods are designed to treat angiogenesis-related disorders, e.g. retinopathy, and thus those of ordinary skill in the art would immediately recognize that the organism is "in need" of treatment (Abstract; [0010]), and that the dsRNA molecule to be 21-23 nucleotides in length are recognized in the art to specifically inhibit gene expression [0129]. Thus, the King reference teaches each and every element of the claim.

9. **Claims 2, 5-10, 13, 19-20, 24, 26-28, 31 and 48-53 stand rejected under 35 U.S.C. 102(e)** as being anticipated by Tolentino et al (U.S. Patent No. 7,148,342 B2).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed February 13, 2009.

Claim interpretation: Applicant claims the method for delivery of oligoribonucleotides comprises introducing "a composition comprising one or more naked double-stranded oligonucleotides (dsRNA). However, the term "comprising" is open-ended and allows for additional, unrecited elements in the claims. MPEP §2111.03 specifically sets forth that the transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and **does not exclude** additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). In the instant case, the specification discloses that the

naked dsRNAs can be introduced into the cells or tissues combined with one or more suitable carriers, e.g. a micellar structure, preferably a liposome (pg 13, ¶1). Thus, the broadest reasonable interpretation of the instant claims reasonably embraces "a composition comprising" a carrier vehicle, e.g. micelle or liposome, encapsulating naked dsRNA molecules.

With respect to claim 2, Tolentino et al discloses a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue (pg 1, [0009]). Tolentino et al disclose the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 13, lines 37-50), and wherein the carrier may comprise a ligand molecule that can target the carrier to a particular cell or tissue (col. 13, lines 56-58).

With respect to claims 5-6, King discloses the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode VEGF, Flt-1 and Flk/KDR genes (col. 2, lines 45-47).

With respect to claims 7-9 and 50-53, Tolentino et al disclose the compositions of the invention are used for the treatment of retinal diseases such as age-related macular degeneration (col. 2, lines 47-50).

With respect to claim 10, Tolentino et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of Tolentino et al reasonably embraces such limitations, absent evidence to the contrary.

With respect to claim 13, Tolentino et al disclose the dsRNA molecules are less than 30 nucleotides, about 19 to about 25 nucleotides, e.g. 21-22 nucleotides (col. 2, lines 8, 25 and 57-58; col. 7, line 15).

With respect to claims 19-20, King discloses the inventive nucleic acids may be inserted into vectors, wherein the expression of the nucleic acid is operably linked to a promoter, e.g. a tissue-specific promoter (col. 9, lines 37-47).

With respect to claim 24, King discloses the carrier may comprise compounds that achieve controlled release, wherein the period over which the agent is administered can be long term, e.g. osmotic pumps, pellets or suppositories (col. 15, lines 28-35).

With respect to claim 26, Tolentino et al disclose the agent may be administered by different routes, e.g. regional or systemic, intravenous (col. 12, line 39; col. 15, lines 15-35).

With respect to claims 27-28 and 31, Tolentino et al disclose the subject may be human (col. 11, line 60).

With respect to claim 48, Tolentino et al disclose the dsRNA comprises two symmetrical 3' overhangs of two nucleotides in length (col. 5, lines 45-60).

With respect to claim 49, Tolentino et al disclose the 3' overhangs may be 2'-deoxythymidine (col. 6, line 3).

Response to Arguments

Applicant argues that the Tolentino reference is not prior art. As acknowledged by the Examiner, the priority date of the present application is April 18, 2002. The Tolentino reference claims priority to a provisional application that was filed July 24, 2002. Accordingly, the Tolentino reference is not prior art against the present application.

Applicant's argument(s) has been fully considered, but is not persuasive. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15 Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

The Examiner acknowledges Applicant's desire to retract the statement made in the previously filed response, which was filed on July 24, 2008 in response to the Office Action mailed January 24, 2008. However, such statements are of record and the Examiner is unaware of a provision by which Applicant may retract said statements of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. **Claims 2-13, 19-20, 24, 26-28, 31, 46 and 48-53 stand rejected under 35 U.S.C. 103(a)** as being unpatentable over Robinson et al (U.S. Patent No. 5,814,620) in view of LaFleur et al (U.S. 6,433,145 B1) and Tuschl et al (U.S. 2002/0086356 A1).

This rejection is maintained for reasons of record in the office action mailed January 24, 2008 and re-stated below. The rejection has been re-worded slightly based upon Applicant's amendment filed February 13, 2009.

Claim interpretation: Applicant claims the method for delivery of oligoribonucleotides comprises introducing "a composition comprising one or more naked double-stranded oligonucleotides (dsRNA). However, the term "comprising" is open-ended and allows for additional, unrecited elements in the claims. MPEP §2111.03 specifically sets forth that the transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and **does not exclude** additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). In the instant case, the specification discloses that the naked dsRNAs can be introduced into the cells or tissues combined with one or more suitable carriers, e.g. a micellar structure, preferably a liposome (pg 13, ¶1). Thus, the broadest reasonable interpretation of the instant claims reasonably embraces "a composition comprising" a carrier vehicle, e.g. micelle or liposome, encapsulating naked dsRNA molecules.

Determining the scope and contents of the prior art.

Robinson et al disclose a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier into cells and/or tissues of the eye, wherein a composition comprising one or more antisense oligoribonucleotides are introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue. The method of the invention is used for the treatment of retinal diseases such as age-related macular degeneration (col. 2, lines 36-37; col. 11, lines 15-20). Robinson et al disclose the method yields a test organism maintained under conditions allowing the degradation of the corresponding target gene mRNA (col. 11, line 30-col. 12, lined 15). The antisense nucleic

acids are from about 15 to about 25 nucleotides in length, and may be chemically modified (col. 3, line 45-col. 4, line 14). The antisense nucleic acids are targeted against a cellular gene such as VEGF, thereby inhibiting expression of VEGF in the retina (col. 4, lines 23-26), and may be administered to the patient, e.g. human, locally or systemically (col. 3, lines 35-37; col. 4, lines 35-42), wherein the formulation may comprise a carrier, e.g. a liposome (col. 9, line 13) and/or slow-release polymers (col. 11, line 13).

Robinson et al do not disclose:
i) the antisense nucleic acid is double-stranded RNA,
ii) the dsRNA nucleic acid is encoded by a vector,
iii) the dsRNA is operably linked to a tissue-specific promoter,
iv) the carrier is specific for the cells and/or tissues, and
v) the method is used in drug discovery or target gene validation.

However, at the time of the invention, LaFleur et al disclosed a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier (col. 9, line 52; col. 102, line 14), wherein the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal model wherein the agent may be administered over a long-term period (col. 77, lines 29-30). Furthermore, the cells may be used to screen for KDI antagonists (col. 138, line 25).

LaFleur et al disclose the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode KDI (col. 140, lined 23), wherein the dsRNA molecules are at least 15 nucleotides, more preferably at least about 20 nucleotides (col. 15, lines 3-4; col. 17 lines 19-20). The antisense approach is used to inhibit translation of endogenous target gene mRNA, e.g. KDI, wherein the oligonucleotides range from about 6 to about 50 nucleotides in length (col. 141, lines 5-8, 15-17), wherein one or more nucleotide bases may be modified (col. 9, lines 60-65; col. 141-142). The inventive nucleic acids may be inserted into vectors and operably linked to a tissue-specific promoter (col.s 75-76; col 101, lines 57-67; col. 140, lines 23-25) and/or may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 76, lines 25-32). Various delivery systems are known and can be used to administer a compound of the invention, e.g. encapsulation in liposome particles, systemically by intravenous or subcutaneous routes, e.g. topical drops and eye drop form, wherein the composition may be provided by continuous subcutaneous infusion, or continuous infusion into the aqueous humor in order to increase the local concentration of the polynucleotide in the retina, wherein the carrier may be specific for the retinal cells, e.g. by targeting a specific receptor (col. 76, lines 25-40; col. 77, line 55; col. 79, lines 32-33; col. 107, line 19; col. 119, line 38). The polynucleotides of the invention may be used in the treatment of cells and/or tissues from the retina (col. 118, lines 35-37; col. 130, lines 37-46), e.g. retinal diseases such as macular degeneration and retinoblastoma (col. 118, lines 35-37).

Neither Robinson et al nor LaFleur et al disclose:

i) the method may be used for the identification or validation of the function of a gene,
ii) the target gene is expressed predominantly or specifically in the eye,
iii) the dsRNA contains two symmetrical 3' overhangs, and
iv) the dsRNA 3' overhangs are 2'-deoxythimidine.

However, at the time of the invention, Tuschl et al disclosed methods of using single-stranded and double-stranded RNA molecules to mediate gene-silencing of a target gene expression to examine the function of a gene, to assess whether an agent acts on a gene and to validate targets for drug discovery (pg 2, [0010]), wherein the phenotype of the test cell or organism is then observed and compared to that of an appropriate control cell or organism (pg 2, [0010-0011]). The single-stranded and double-stranded RNA molecules are about 21 to about 23 nucleotides, wherein both strands of the dsRNA have a 3' overhang of two nucleotides, wherein the 3' overhang nucleotides may be substituted for 2'-deoxythymidine (pg 5, [0055]). Tuschl et al disclose that any cellular gene, e.g. an oncogene or the mRNA of any protein associated with or causative of a disease or undesirable condition, can be targeted for degradation using gene-silencing RNAs (pg 6, [0061]).

Ascertaining the differences between the prior art and the claims at issue.

LaFleur et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue anatomically comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of LaFleur et al reasonably embraces such limitations, absent evidence to the contrary.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in designing, formulating and administering gene-silencing RNA nucleic acids to mammalian subjects, as well as anatomical and physiological knowledge of the circulatory and ocular organ systems. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute an antisense gene-silencing RNA as taught by Robinson et al with a double-stranded gene-silencing RNA as taught by LaFleur et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. One of ordinary skill in the art recognized that, in general, siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligonucleotides can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell (Tuschl et al). Thus, in this sense, siRNAs and antisense oligonucleotides are art-recognized equivalents that may be used for the same purpose:

reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.) An artisan would be motivated to substitute gene-silencing antisense RNAs for gene-silencing dsRNA or a vector expressing a gene-silencing dsRNA because dsRNAs are extraordinarily powerful reagents for mediating gene silencing and are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (see for example, Tuschl et al, Figures 8A and 8B).

It also would have been obvious to try administering a gene-silencing dsRNA targeted against a disease-causing gene that is predominantly or specifically expressed in the eye because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." At the time of the invention, those of ordinary skill in the art were well aware that gene-silencing dsRNAs may be designed to target a disease-causing mRNA for degradation. An artisan would be motivated to try administering a gene-silencing dsRNA targeted against a disease-causing gene that is predominantly or specifically expressed in the eye because the patient would be less likely to suffer from adverse, non-specific side effects due to off-target responses in non-retinal cells while simultaneously achieving degradation of the intended target gene, thereby treating the disease or disorder that the patient is suffering from.

It also would have been obvious to combine the method of inhibiting the expression of a target gene in a retinal cell to further provide for a test cell, tissue or organism from which to identify or validate the function of a gene with a reasonable expectation of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Furthermore, LaFleur et al and Tuschl et al disclose that methods of using gene-silencing RNAs may be used is gene and drug discovery and validation assay methods. An artisan would be motivated to use gene-silencing dsRNAs in gene and drug discovery and validation assay methods because it is technically easier and less costly to temporarily silence a novel gene with a specific dsRNA than it is to generate a genetically-modified genomic loss-of-function cell, tissue or organism for each and every gene the artisan wishes to assay in the screening methods.

Thus, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that:

a) the Office alleges that siRNA and antisense are equivalents. The Office, however, has failed to provide a single reference showing that antisense and siRNA are equivalents. For example, the Office states that both siRNA and antisense inhibit gene expression. However, the fact that two different classes of compounds inhibit gene expression does not make the compositions equivalents. As acknowledged by the Office, siRNA and antisense work by *"different* biochemical mechanisms" (Office Action, p. 24, emphasis added). The fact that the

compositions work by "different" mechanisms indicates that antisense and dsRNA are not equivalents. Therefore, the present invention is not a mere substitution and, thus, the Office has failed to make a proper *prima facie* obviousness rejection;

b) the Office has failed to provide a reference or a combination of references showing that antisense and dsRNA can be substituted for one another without any changes and provide a reasonable expectation of success;

c) prior to the present invention one of skill in the art would not have had a reasonable expectation of success that it would have been possible to traffic a dsRNA composition across the blood-brain or blood-retina barrier because it has been stated [specification] that it was "very difficult." Conclusory statements by the Office that there would have been a reasonable expectation of success without pointing out why there would have been a reasonable expectation of success are insufficient; and

d) the Office has also not demonstrated that someone intending to traffic naked dsRNA across the blood-brain or blood-retina barrier would have had a reasonable expectation of success. There is no indication that dsRNA can even cross the blood-brain or the blood-retina barrier.

Applicant's argument(s) has been fully considered, but is not persuasive.

With respect to a), the intended purpose of the dsRNA molecule is to modulate or inhibit expression of the target gene(s) in the eye (specification, pg 1, line 1; Claim 5). Thus, the nature of the problem to be solved is to reduce target gene expression. One of ordinary skill in the art recognized that, in general, siRNAs (small, 21-23 nucleotide dsRNA molecules) and antisense oligonucleotides can be used to produce the same effect, to wit, sequence-specific gene silencing, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligonucleotides can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell (Tuschl et al). Tuschl et al disclose that dsRNA undergoes strand separation, wherein the antisense strand directs sequence-specific gene silencing (e.g. Figure 11). Thus, the dsRNA necessarily acts via an antisense mechanism to effect gene-silencing, and siRNAs and antisense oligonucleotides are art-recognized equivalents that

may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.) The biological machinery [mechanism] by which the cell uses siRNA/dsRNA and antisense molecules to modulate or inhibit gene expression naturally flows from the structure of gene-silencing RNA molecule. While this may be different between siRNA/dsRNA and antisense molecules, the result [problem to solve] is the same: expression of the target gene(s) is modulated or inhibited. Thus, the Examiner maintains the position that it would have been obvious to one of ordinary skill in the art to substitute an antisense gene-silencing RNA as taught by Robinson et al with a double-stranded gene-silencing RNA as taught by LaFleur et al with a reasonable expectation of success because the simple substitution of a first gene-silencing RNA molecule for another gene-silencing RNA molecule would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

With respect to b), Applicant appears to have overlooked that Tuschl et al disclose that dsRNA undergoes strand separation, wherein the antisense strand directs sequence-specific gene silencing (e.g. Figure 11). Thus, the dsRNA necessarily acts via an antisense mechanism to effect gene-silencing, wherein those of ordinary skill in the art would have a reasonable expectation of success in the ability to modulate or inhibit the expression of a target gene when substituting a first gene-silencing molecule, e.g. antisense, with a second gene-silencing molecule, e.g. dsRNA, because both such gene-silencing molecules, by definition, were recognized in the art to successfully modulate or inhibit the expression of a target gene.

With respect to c-d), as a first matter, Applicant claims the method for delivery of oligoribonucleotides comprises introducing "a composition comprising one or more naked double-stranded oligonucleotides (dsRNA). However, the term "comprising" is open-ended and allows for additional, unrecited elements in the claims. MPEP §2111.03 specifically sets forth that the transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004). In the instant case, the specification discloses that the naked dsRNAs can be introduced into the cells or tissues combined with one or more suitable carriers, e.g. a micellar structure, preferably a liposome (pg 13, ¶1). Thus, the broadest

reasonable interpretation of the instant claims reasonably embraces "a composition comprising" a carrier vehicle, e.g. micelle or liposome, encapsulating the dsRNA molecules.

As a second matter, the specification fails to disclose a definition for the term "naked". Absent evidence to the contrary, dsRNA molecules encapsulated within a liposome or micelle are reasonably interpreted to be "naked" to the extent that said dsRNA molecules are not covalently modified with some other agent(s), e.g. proteins, within said liposome or micelle.

As a third matter, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) In the instant case, Robinson et al disclose a method for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier into cells and/or tissues of the eye, wherein a composition comprising one or more gene-silencing oligoribonucleotides are introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue. The method of the invention is used for the treatment of retinal diseases such as age-related macular degeneration, and may be administered to the patient locally or systemically, wherein the formulation may comprise a carrier, e.g. a liposome and/or slow-release polymers. LaFleur et al disclosed a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more gene-silencing oligoribonucleotides (dsRNA) is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. Various delivery systems are known and can be used to administer a compound of the invention, e.g. encapsulation in liposome particles, systemically by intravenous or subcutaneous routes, e.g. topical drops and eye drop form, wherein the composition may be provided by continuous subcutaneous infusion, or continuous infusion into the aqueous humor in order to increase the local concentration of the polynucleotide in the retina, wherein the carrier may be specific for the retinal cells. The polynucleotides of the invention may be used in the treatment of cells and/or tissues from the retina, e.g. retinal diseases such as macular degeneration and retinoblastoma. Thus, in light of the prior art teaching the formulation of a

composition comprising gene-silencing oligoribonucleotides for the purpose of treating a retinal disease, wherein the composition may be administered either locally or systemically outside the blood-brain or the blood-retina barrier, it is the Examiner's position that the ordinary artisan would have a reasonable expectation of success for delivery of oligoribonucleotides across the blood-brain or the blood-retina barrier into cells and/or tissues of the eye.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633